A. BACKGROUND AND RATIONALE FOR THE TRIAL

A.1 Title of study: "Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy using Autologous Unmodified and Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals"

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A.2 This clinical protocol proposes to examine the safety, migration to lymph nodes, duration of *in vivo* persistence and antiviral activity of adoptively transferred unmodified and genetically modified autologous HIV-specific $CD8^+$ cytotoxic T lymphocytes (CTL) in HIV seropositive patients. This study is a follow-up to a study which evaluated the adoptive transfer of autologous $CD8^+$ HIV-specific CTL clones modified to express a marker/suicide gene (hygromycin phosphotransferase-HSV thymidine kinase (HyTK)) under BB-IND 4337 (FHCRC Protocol #827.0). Although there were no serious toxicities in this initial study, 5 of the 6 patients treated developed T cell immune responses to HyTK and had poor persistence of CTL at the highest doses of transfused CTL. In the study proposed here, 8 patients will receive 3 infusions of unmodified $CD8^+$ CTL clones in a cell dose escalation scheme to establish safety, followed by 2 infusions of $CD8^+$ CTL modified by retrovirus-mediated gene transfer to contain the neomycin phosphotransferase marker gene (*neo*) to facilitate analysis of the migration of transferred T cells to lymph nodes and to determine if *neo* is immunogenic. If immune responses specific for *neo* do not develop the long term persistence of transferred CTL can be evaluated by PCR for the marker gene. If immune responses to *neo* do develop, we will evaluate long term *in vivo* persistence of unmodified CTL using T cell receptor gene rearrangements in a subset of the 8 patients.

B. SIMILARITY TO OTHER RAC-APPROVED PROTOCOLS

B.1 No.

B.2 The proposed study is similar to a prior clinical trial, submitted to and approved by the RAC, and conducted by Stanley Riddell, M.D., entitled: "Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy using Genetically Modified Autologous CD8+ HIV-Specific T Cells in HIV Seropositive Individuals" (BB-IND 4337/FHCRC Protocol #827.0).

C. VECTOR, TARGET CELL, AND TRANSDUCTION PROCEDURES

C.1 The LN vector is identical to the LNL6 vector with the exception that bases 2329 to 3009 of LNL6 have been precisely removed to generate LN. These sequences include 3' non-coding *neo* gene sequences and all of the retroviral *env* sequences that remained in LNL6. The lack of homologous overlap between the vector LN and viral DNA in the PA317 packaging cells excludes the possibility of helper virus generation by homologous recombination and further increases the safety of the LN vector for use in humans.

The PA317 cell line secretes the LN retrovirus at a concentration of at least $1x10^5$ G418 resistant colony forming units per ml ($G418^R$ CFU/ml). Targeted Genetics Corporation